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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,156	05/26/1999	MICHAEL ROSENBLUM	D5425CIP2	4227

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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 05/23/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/320,156

Applicant(s)
Rosenblum et al

Examiner
Karen Canella

Art Unit
1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 months MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above, claim(s) 1-14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.
2. Claims 1-14 remain withdrawn from consideration. Claims 15-19 are under consideration.

Claim Rejections Maintained

3. The rejection of claims 15 and 19 under 35 U.S.C. 103(a), as being unpatentable over Bacus et al (USP 5,514,554, effective filing date 9/27/91) in view of Rosenblum et al (Cancer Communications, 1991) and Hudziak et al (Molecular and Cellular Biology, 1989), is maintained for reasons of record.

Applicant argues that ricin and TNF are obtained from widely different sources and have widely different mechanisms of action, therefore the effect of substituting TNF for ricin in an antibody conjugate cannot be anticipated. This has been considered but not found persuasive as Hudziak teaches that TNF administered concurrently with an antibody directed to the extracellular portion of the erbB2 receptor, thus demonstrating that TNF can act as a toxin to breast cancer cells having an anti-erbB2 antibody bound to the extracellular portion of said receptor. Rosenblum also teaches that an immunotoxin comprising TNF conjugated to an anti-melanoma target was toxic to melanoma cells. Thus both Hudziak and Rosenblum teach the administration of TNF by means of separate or conjugate administration with an antibody directed to the cellular target for achieving toxicity to tumor cells.

Applicant argues that Bacus teaches that the antibodies used be specific for an epitope on the extracellular domain of erbB2. This has been considered but not found persuasive, as the instant claims to a composition comprising an anti-erbB2 antibody conjugated to TNF, wherein the antibody specifically binds an extracellular epitope of erbB2 do not have limitations that would exclude the antibody of Baccus.

Applicant further argues that Baccus does not disclose information on the morbidity of normal cells in the course of conjugate usage. This is not found persuasive, as the instant claims

do not contain embodiments regarding the relative morbidity of breast cancer cells versus normal breast cells. Further, Baccus teaches the anti-erbB2-ricin conjugate as being useful as a therapeutic agent (column 4, lines 10-15) which retards tumor growth (Figure 6).

Applicant argues that the anti-melanoma TNF conjugate taught by Rosenblum does not render obvious the instant claims due to the differences in characteristics of a melanoma cell line and the carcinoma cell lines of the instant invention. This is not found persuasive. Rosenblum teaches that conjugation of TNF to an antibody via SPDP chemistry does not disrupt the binding characteristic of the antibody, therefore the antibody of Rosenblum serves as a targeting moiety for the TNF to melanoma cells.

4. The rejection of claims 15-19 under 35 U.S.C. 103(a), as being unpatentable over Wels et al (USP 5,571,894, effective filing date 7/15/91) in view of Hoogenboom et al (Biochimica et Biophysica Acta, 1991, Vol. 4, pp. 345-354 and Hudziak et al (Molecular and Cellular Biology, 1989), is maintained for reasons of record. Applicant puts forth the argument that one of skill in the art would not be able to predict with certainty the effectiveness of an anti-erbB2-TNF conjugate against target cells for similar reasons as used to argue the rejection above. This is not found persuasive.

Wels teaches an anti erbB2 antibody which is a single chain antibody, fused to a plant bacterial toxin. Hoogenboom teaches a single chain antibody-TNF fusion protein. Applicant argues the same point against the combination of Wels and Hoogenboom and Hudziak as above. It is not found persuasive for the reasons set forth above, namely that Wels teaches that a single chain antibody can be fused to a bacterial toxin and retain the binding activity of the antibody as well as the toxic activity associated with anti-ribosomal plant toxins. Hoogenboom teaches that TNF can be fused to a single chain antibody with retention of the antibodies binding activity, and the retention of TNF activity, and the resulting immunotoxin is useful as a toxic agent against myeloma cells. Hudziak teaches the efficacy of providing TNF simultaneous to anti erbB2 in the treatment of breast cancer cells. Thus, one of skill in the art would be motivated to make an immunotoxin to target breast cancer cells by the fusion of an anti-erbB2 antibody to TNF from

the teachings of Wels and Hudziak. One of skill in the art would have reasonable expectation of success from the teachings of Hoogenboom on the retention of binding and TNF activity in the anti-myeloma TNF immunotoxin.


Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
May 6, 2002


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